Minutes of Meeting

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee

August 11, 2010

Members Present: Chair, Dr. Lucy Culpepper, Ms. Janet Allen, Dr. Gerard Ferris, Dr. Kelli Littlejohn, Mr. Ben Main, Dr. Robert Moon, Ms. LaTonage Porter, Dr. Nancy Sawyer, Dr. Joseph Thomas and Dr. Chivers Woodruff

Members Absent: Dr. Michelle Freeman

Presenters: Dr. Tina Hisel

Presenters Present via teleconference: Dr. Laureen Biczak

1. OPENING REMARKS

Dr. Culpepper called the Pharmacy and Therapeutics (P&T) Committee Meeting to order at 9:00 a.m.

2. APPROVAL OF MINUTES

Chairman Culpepper asked if there were any corrections to the minutes from the May 12, 2010 P&T Committee Meeting. A correction was made by Dr. Culpepper on page 8 (change 'as' to 'is'). A correction was also made by Dr. Ferris on page 4 (change 'second generation antihistamines' to 'first generation antihistamines').

There were no objections. Dr. Woodruff made a motion to approve the minutes with corrections and Mr. Main seconded to approve the minutes with corrections. The corrected minutes were unanimously approved.

3. PHARMACY PROGRAM UPDATE

Dr. Littlejohn noted that a routine Preferred Drug List (PDL) update was completed on July 1, 2010.

An ALERT was sent to providers in July 2010 outlining the identification of oil-spill related illnesses/injuries for Medicaid recipients. In order to track and evaluate health outcomes and costs related to the BP Oil Spill, the Alabama Medicaid Agency will begin use of claims billing indicators to identify services provided to Alabama Medicaid recipients when treated for an oil-spill related illness or injury.

The Agency encourages providers to visit the website (www.medicaid.alabama.gov) to receive various on-line publications, including Medicaid Matters. Providers can also join Alabama Medicaid's e-mail list to learn more about important issues, such as Health Care Reform.

The Agency is working toward the reimbursement modification to the Average Acquisition Cost (AAC) Program, which is pending CMS final approval. That is scheduled to be implemented on August 13, 2010.

4. ORAL PRESENTATIONS BY MANUFACTURERS/MANUFACTURERS' REPRESENTATIVES

Five-minute verbal presentations were made on behalf of pharmaceutical manufacturers. The process and timing system for the manufacturers' oral presentations was explained. The drugs and corresponding manufacturers are listed below with the appropriate therapeutic class. There were a total of eight manufacturer verbal presentations at the meeting.

5. PHARMACOTHERAPY CLASS REVIEW(S) (Please refer to the website for full text review(s).)

The pharmacotherapy class reviews began at approximately 9:06 a.m. There was one new drug class review.

Genitourinary Smooth Muscle Relaxants: American Hospital Formulary Service (AHFS) 861200
Manufacturer comments on behalf of these products:
VESIcare® - Astellas

Dr. Hisel commented that urinary incontinence and overactive bladder (OAB) cause both physical and psychological morbidity, as well as adversely impact quality of life. Normal voiding is dependent on acetylcholine-induced stimulation of muscarinic receptors on bladder smooth muscle and OAB is often the result of overactivity of the detrusor muscle. Initial treatment options include lifestyle modifications, behavioral therapy and pharmacologic therapy. The genitourinary smooth muscle relaxants are muscarinic receptor antagonists. They are approved for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency. There are 5 different muscarinic receptor subtypes found throughout the body, including the central nervous system, salivary glands, heart, gastrointestinal tract, bladder, tear ducts, and blood vessels. Although some of the genitourinary smooth muscle relaxants are more selective for muscarinic receptors found in the bladder, it is unclear if this translates into better tolerability or efficacy. The agents that are included in this review are listed in Table 1. Flavoxate, oxybutynin immediate-release syrup/tablet, as well as oxybutynin extended-release tablets are available in a generic formulation.

Current treatment guidelines that incorporate the use of the genitourinary smooth muscle relaxants are summarized in Table 2. Antimuscarinic agents are the primary treatment for patients with OAB symptoms, in addition to lifestyle modifications and behavioral therapy. In general, the guidelines do not give preference to one particular agent over another.

In clinical trials, the genitourinary smooth muscle relaxants have been shown to modestly improve urinary symptoms, including frequency, urgency, nocturia and incontinence episodes. The majority of the studies were 6 to 12 weeks in duration; however, a few long-term, open-label studies have also been conducted. The majority of the active-controlled studies compared oxybutynin and tolterodine. There were very few active-controlled studies found in the medical literature with flavoxate, darifenacin, fesoterodine, solifenacin or trospium. Several studies have demonstrated similar efficacy with the genitourinary smooth muscle relaxants for most, but not all, of the endpoints assessed. In general, studies directly comparing immediate-release (IR) and extended-release (ER) formulations of the same drug found no differences in efficacy. Studies directly comparing IR formulations of different drugs, as well as studies comparing ER formulations of different drugs, have also demonstrated similar efficacy. Very few studies have demonstrated greater efficacy with one genitourinary smooth muscle relaxant over another. The use of the genitourinary smooth muscle relaxants for the treatment of OAB has also been associated with an improvement in quality of life.

Adverse events occur frequently with the genitourinary smooth muscle relaxants due to their anticholinergic effects, which often leads to discontinuation of therapy. The most common adverse events include dry mouth, blurred vision, abdominal discomfort, drowsiness, nausea and dizziness. These agents may also cause confusion or memory impairment in the elderly. The incidence of adverse events varies among the agents and depends upon the formulation used (ER, IR or transdermal). Adverse events tend to be higher with the IR formulations compared to ER formulations. In general, dry mouth occurs at a higher rate with oxybutynin than with the other agents.

Dr. Hisel concluded that there is insufficient evidence to support that one brand genitourinary smooth muscle relaxant is more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand genitourinary smooth muscle relaxants within the class reviewed are comparable to each other and to the generics and OTC products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

No brand genitourinary smooth muscle relaxant is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

There were no further discussions on the agents in this class. Dr. Culpepper asked the P&T Committee Members to mark their ballots.

6. PHARMACOTHERAPY CLASS RE-REVIEWS (Please refer to the website for full text reviews.)

Platelet-Aggregation Inhibitors: AHFS 201218
Manufacturer comments on behalf of these products:
Plavix® - Sanofi-Aventis
Effient® - Eli Lilly & Co.

Dr. Hisel commented that the platelet-aggregation inhibitors that are included in this review are listed in Table 1. Prasugrel was approved by the FDA since this class was last reviewed. The platelet-aggregation inhibitors play a major role in the management of cardiovascular, cerebrovascular and peripheral vascular diseases. They are approved for the treatment and/or prevention of acute coronary syndromes (ACS), angina, intermittent claudication, myocardial infarction, stroke and transient ischemic attack (TIA). They are also approved for the prevention of thrombosis in patients undergoing cardiovascular procedures and/or surgery. Aspirin, cilostazol, dipyridamole and ticlopidine are available in a generic formulation. Aspirin is also available over-the-counter.

There are numerous guidelines that incorporate the use of the platelet-aggregation inhibitors. Aspirin has been the most frequently studied agent. It is recommended for the primary prevention of cardiovascular disease in men 45 to 79 years of age and in women 55 to 79 years of age. Aspirin is also recommended for the treatment of ACS, chronic stable angina, peripheral artery disease, non-cardioembolic stroke, TIA and for the secondary prevention of coronary artery disease. For patients who have experienced a non-cardioembolic stroke or TIA, treatment with aspirin, the combination of aspirin and extended-release dipyridamole, and clopidogrel are all acceptable options for initial therapy. However, the combination of aspirin and extended-release dipyridamole or clopidogrel monotherapy are suggested over aspirin monotherapy. Dual antiplatelet therapy with aspirin and clopidogrel is recommended for the treatment of non-ST-segment elevation ACS, ST-segment elevation myocardial infarction, and for the treatment of patients who undergo percutaneous coronary intervention (PCI) with stenting. The majority of the guidelines do not provide recommendations regarding the use of prasugrel. However, the 2009 ACC/AHA guidelines recommend aspirin in combination with either clopidogrel or prasugrel for patients with ST-segment elevation myocardial infarction who undergo PCI with stenting and do not give preference to one regimen over another.

A variety of clinical trials have assessed the effects of the platelet-aggregation inhibitors on cardiovascular, cerebrovascular and peripheral artery disease outcomes. In patients with a history of ischemic stroke or TIA, treatment with the combination of aspirin and extended-release dipyridamole, clopidogrel monotherapy, or ticlopidine monotherapy significantly decreased thrombotic events compared to aspirin monotherapy. In the PROFESS trial, there was no significant difference in the rate of recurrent stroke with clopidogrel compared to the combination of aspirin and extended-release dipyridamole. Dipyridamole monotherapy has been shown to reduce stroke recurrence compared to placebo, but has not been shown to be more effective than aspirin monotherapy. Treatment with the combination of clopidogrel and aspirin significantly decreased morbidity and mortality in patients with ACS compared to aspirin monotherapy. The TRITON-TIMI 38 trial compared the efficacy and safety of clopidogrel or prasugrel in

combination with aspirin in patients with ACS undergoing PCI. Treatment with prasugrel was associated with a significant reduction in the composite of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke compared to clopidogrel. Overall mortality did not differ among the treatment groups. Stent thrombosis occurred in 2.4% of patients treated with clopidogrel and 1.1% of patients receiving prasugrel. However, significantly more patients treated with prasugrel had major bleeding, including life-threatening and fatal bleeding, compared to patients who received clopidogrel.

Clopidogrel forms less of the active metabolite and has a smaller effect on platelet function in patients who are CYP2C19 poor metabolizers. Prasugrel can cause significant bleeding and should not be used in patients with active bleeding or a history of TIA or stroke. It is also not recommended in patients ≥75 years of age due to the increased risk of fatal and intracranial bleeding. Because ticlopidine is associated with a risk of life-threatening blood dyscrasias, it should be reserved for patients who are intolerant or allergic to aspirin therapy or who have failed aspirin therapy.

Dr. Hisel concluded that all brand platelet-aggregation inhibitors within the class reviewed are comparable to each other and to the generics and OTC products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use. Clopidogrel and the fixed-dose combination of aspirin and extended-release dipyridamole should be available as first-line therapy through the medical justification portion of the prior authorization process for patients who have experienced an ischemic stroke or TIA. Clopidogrel and prasugrel should be available as first-line therapy (in combination with aspirin) through the medical justification portion of the prior authorization process for patients who have experienced an acute coronary syndrome who are going to be managed medically or with percutaneous coronary intervention.

No brand platelet-aggregation inhibitor is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

Dr. Woodruff asked if all proton-pump inhibitors are contraindicated with clopidogrel or just omeprazole. Dr. Hisel replied that there are two contraindications listed in the prescribing information for clopidogrel: 1) active pathological bleeding, such as peptic ulcer or intracranial hemorrhage; and 2) hypersensitivity to clopidogrel. Dr. Woodruff stated that in the oral presentation summary, it is recommended to avoid concomitant use of clopidogrel with drugs that inhibit CYP2C19. He asked if this was a class effect with other proton-pump inhibitors. Dr. Biczak replied that the FDA issued a statement concerning omeprazole and clopidogrel in November 2009, which suggested that omeprazole should be avoided until more data becomes available. Esomeprazole is similar to omeprazole; therefore, concerns have been raised regarding this agent as well. However, the evidence is not clear for either product at this time.

Dr. Ferris asked that, if a patient needs an anti-inflammatory and analgesic agent, could the dose of aspirin be increased instead of adding a nonsteroidal anti-inflammatory drug (NSAID). Dr. Hisel replied that the dose of aspirin could be increased; however, there is an increased risk of bleeding. Dr. Ferris asked about the potential drug interaction with aspirin and NSAIDs regarding the timing

of administration. Dr. Hisel replied that she did not have specific information regarding the timing of administration of aspirin and NSAIDs.

Mr. Main asked for further information regarding a European study, which compared low-dose enteric-coated aspirin and regular strength enteric-coated aspirin. Dr. Hisel replied that she did not have specific information on that study.

Dr. Littlejohn stated that, Lori Thomas, a pharmacy student, is completing a drug information rotation with the Agency. She requested that the Committee allow Ms. Thomas to research the three questions and formulate an answer, which will be distributed via e-mail. Dr. Littlejohn clarified the three previous questions asked by the Committee.

Dr. Sawyer asked if the fixed-dose combination of aspirin/dipyridamole was available generically. Dr. Hisel replied that it is not available in a generic formulation.

There were no further discussions on the agents in this class. Dr. Culpepper asked the P&T Committee Members to mark their ballots.

Antiarrhythmic Agents: AHFS 240404
Manufacturer comments on behalf of these products:
None

Dr. Hisel commented that the antiarrhythmic agents are effective for the treatment of atrial fibrillation/flutter and ventricular arrhythmias. The agents that are included in this review are listed in Table 1. Dronedarone was approved by the FDA since this class was last reviewed. All of the antiarrhythmic agents are available in a generic formulation, with the exception of dofetilide and dronedarone.

Current treatment guidelines that incorporate the use of the antiarrhythmic agents are summarized in Table 2. Treatment options for atrial fibrillation include anticoagulation, ventricular rate control and drug therapy to maintain sinus rhythm. The AFFIRM, RACE and HOT CAFE trials demonstrated similar outcomes with rate control compared to rhythm control strategies. Rate control may be preferred for older patients with persistent atrial fibrillation who have hypertension or heart disease. Rhythm control may be preferred in younger patients with lone atrial fibrillation or in those whose quality of life has been affected. Ideally, antiarrhythmic agents should reduce symptoms, prevent recurrent atrial fibrillation and have a low incidence of toxicity. However, all of the antiarrhythmic agents can cause serious complications. Initial and long-term management strategies differ from one patient to another. The specific antiarrhythmic agent that is recommended for the treatment of atrial fibrillation depends upon the patient's comorbidities and cardiac history, as well as adverse effects. The antiarrhythmic agents are generally not recommended for the initial treatment of ventricular arrhythmias; however, they may be effective as adjunctive therapy in certain situations. These agents have not been shown to improve mortality in patients with atrial or ventricular arrhythmias.

Amiodarone is an effective treatment option for atrial fibrillation; however, its use is limited by toxicity, photosensitivity reactions and bluish discoloration of the skin. Amiodarone is associated

with a low risk of proarrhythmia in patients with left ventricular hypertrophy, heart failure, coronary artery disease and previous myocardial infarction.

Studies support the efficacy of dofetilide for the prevention of atrial fibrillation/flutter. To reduce the risk of early proarrhythmia, dofetilide must be initiated in the hospital. Dofetilide is available only to hospitals and prescribers who have received appropriate dofetilide dosing and treatment initiation education.

Dronedarone is less lipophilic and has a shorter half-life than amiodarone. Clinical trials have shown that dronedarone reduces the risk of recurrent atrial fibrillation/flutter and is effective for the long-term maintenance of sinus rhythm. However, the ANDROMEDA trial was terminated early due to an excess number of deaths in patients with heart failure who received dronedarone. Death from any cause occurred in 8.1% of patients receiving dronedarone and 3.8% of patients receiving placebo. As a result, dronedarone is contraindicated in patients with New York Heart Association (NYHA) class IV heart failure or NYHA class II to III heart failure with a recent decompensation requiring hospitalization or referral to a specialized heart failure clinic. In a comparative study, dronedarone was found to be less effective than amiodarone for the composite end point of atrial fibrillation recurrence or premature drug discontinuation for intolerance or lack of efficacy. There were fewer thyroid and neurological adverse events with dronedarone, as well as fewer patients discontinuing therapy due to adverse events compared to amiodarone. There were no studies found in the medical literature which evaluated the use of dronedarone for the prevention or treatment of ventricular arrhythmias.

Dr. Hisel concluded that there is insufficient evidence to support that one brand antiarrhythmic agent is more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand antiarrhythmic agents within the class reviewed are comparable to each other and to the generics and OTC products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

No brand antiarrhythmic agent is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

There were no further discussions on the agents in this class. Dr. Culpepper asked the P&T Committee Members to mark their ballots.

Cardiotonic Agents: AHFS 240408
Manufacturer comments on behalf of these products:
None

Dr. Hisel commented that digoxin is the only cardiotonic agent in this class and the injection, solution and tablets are all available in a generic formulation. There have been no major changes in the prescribing information, treatment guidelines or clinical studies since this class was last reviewed.

Therefore, all brand cardiotonic agents within the class reviewed are comparable to each other and to the generics and OTC products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

No brand cardiotonic agent is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

Dr. Littlejohn informed the Committee that there was a recall of generic digoxin since this class was last reviewed. The Agency responded in a timely manner by allowing the brand product to be a preferred agent.

There were no further discussions on the agents in this class. Dr. Culpepper asked the P&T Committee Members to mark their ballots.

Cardiac Drugs, Miscellaneous: AHFS 240492
Manufacturer comments on behalf of these products:
None

Dr. Hisel commented that ranolazine is the only miscellaneous cardiac drug in this class and it is not available in a generic formulation. At the time this class was last reviewed, ranolazine was not approved for use as initial therapy for the treatment of chronic angina. It was to be reserved for patients who had not achieved an adequate response with other antianginal drugs due to its ability to prolong the QT interval. Based on additional clinical data, ranolazine is now approved for the treatment of chronic angina without any further restrictions. The anti-ischemic and antianginal effects do not depend upon reductions in heart rate or blood pressure. It may be used in combination with β-blockers, nitrates, calcium channel blockers, antiplatelet therapy, lipid lowering therapy, ACE inhibitors and angiotensin receptor blockers.

There are several organizations that provide recommendations on the treatment of chronic angina. β-blockers are considered first-line therapy for reducing symptoms of angina in patients with coronary artery disease. Long-acting calcium channel blockers or long-acting nitrates may be used in combination with β-blockers if initial therapy is not successful, or if β-blockers are contraindicated. The available guidelines do not provide specific recommendations regarding the use of ranolazine for the treatment of chronic angina, as it was either approved by the FDA after their publication dates or it has not been approved in their host countries. The ACC/AHA guideline on unstable angina (UA) and non-ST-segment elevation myocardial infarction (NSTEMI) states that ranolazine may be safely administered for symptom relief after UA/NSTEMI, but it does not appear to significantly improve the underlying disease.

Three studies have evaluated the efficacy and safety of sustained-release ranolazine in patients with chronic angina. Ranolazine, administered either as monotherapy or in combination with other anti-anginal drugs, was more effective than placebo with regards to exercise duration, time to onset of angina, frequency of angina and nitroglycerin use. In the MERLIN-TIMI 36 trial, there was no beneficial effect on cardiovascular outcomes with ranolazine compared to placebo in patients with

acute coronary syndrome. Ventricular arrhythmias were less common with ranolazine; however, this did not lead to a reduction in mortality, arrhythmia hospitalization or arrhythmia symptoms. Tolerance to ranolazine did not develop after 12 weeks of therapy. Rebound increases in angina, as measured by exercise duration, have not been observed following abrupt discontinuation of ranolazine.

Dr. Hisel concluded that there is insufficient evidence to support that ranolazine is safer or more efficacious than other agents commonly used for the treatment of chronic angina. Since ranolazine is not recommended as first-line therapy for the treatment of chronic angina, it should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand miscellaneous cardiac drugs within the class reviewed are comparable to each other and to the generics and OTC products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

No brand miscellaneous cardiac drug is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

There were no further discussions on the agents in this class. Dr. Culpepper asked the P&T Committee Members to mark their ballots.

Bile Acid Sequestrants: AHFS 240604
Manufacturer comments on behalf of these products:
None

Dr. Hisel commented that the bile acid sequestrants that are included in this review are listed in Table 1. The bile acid sequestrants are approved as an adjunct to diet and exercise to reduce total and LDL cholesterol. In addition, cholestyramine is indicated to relieve pruritus associated with partial biliary obstruction. Colesevelam is also indicated for the treatment of type 2 diabetes mellitus. Bile acid sequestrants can lower LDL-C by 15% to 30% and raise HDL-C by 3% to 5%. Serum triglyceride levels may increase or remain unchanged. Cholestyramine and colestipol are available in a generic formulation.

Guidelines for the treatment of lipid disorders identify LDL-C as the primary target of cholesterol lowering therapy. The HMG-CoA reductase inhibitors (statins) are generally considered first-line therapy in addition to therapeutic lifestyle changes. For patients who cannot achieve LDL-C goals with the use of a statin alone, the addition of another LDL-C lowering drug such as niacin, a bile acid sequestrant or ezetimibe is recommended. For the treatment of type 2 diabetes, metformin is recommended as first-line therapy due to its efficacy and safety. According to the AACE/ACE algorithm, an incretin mimetic or a DPP-4 inhibitor is the preferred second agent to use in combination with metformin. The combination of metformin and colesevelam is considered an alternative treatment option. This regimen has a minimal risk of hypoglycemia, and colesevelam also lowers LDL-C. Pruritus is a complication of primary biliary cirrhosis and cholestyramine is the drug of choice for the treatment of this complication. Guidelines do not give preference to one bile acid sequestrant over another.

Clinical trials have demonstrated that the bile acid sequestrants can effectively lower LDL-C, non-HDL-C, total cholesterol and positively impact other lipid/lipoprotein parameters. There are very few trials that directly compare the efficacy and safety of these agents. Treatment with cholestyramine led to a 19% reduction in the risk of fatal and non-fatal myocardial infarction in the Lipid Research Clinics Coronary Primary Prevention Trial. Positive cardiovascular outcomes have also been detected in clinical trials which combined bile acid sequestrants with other lipid-modifying drugs. The efficacy of colesevelam as monotherapy for the treatment of type 2 diabetes has not been assessed. When added to existing diabetic regimens, colesevelam lowered the A1C by 0.3% to 0.6% compared to the addition of placebo.

Dr. Hisel concluded that there is insufficient evidence to support that one brand bile acid sequestrant is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand bile acid sequestrants within the class reviewed are comparable to each other and to the generics and OTC products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

No brand bile acid sequestrant is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

Dr. Moon asked if colesevelam is also included in the diabetic class reviews. Dr. Hisel replied that its primary AHFS classification is a bile acid sequestrant; therefore, it is only included in this review.

There were no further discussions on the agents in this class. Dr. Culpepper asked the P&T Committee Members to mark their ballots.

Cholesterol Absorption Inhibitors: AHFS 240605
Manufacturer comments on behalf of these products:
Zetia® - Merck

Dr. Hisel commented that ezetimibe is the only cholesterol absorption inhibitor in this class and it is not available in a generic formulation. It is approved for the treatment of primary hypercholesterolemia, mixed hyperlipidemia, homozygous familial hypercholesterolemia and homozygous familial sitosterolemia.

Guidelines for the treatment of lipid disorders identify LDL-C as the primary target of cholesterol lowering therapy. The HMG-CoA reductase inhibitors (statins) are generally considered first-line therapy in addition to therapeutic lifestyle changes. For patients who cannot achieve LDL-C goals with the use of a statin alone, the addition of another LDL-C lowering drug such as niacin, a bile acid sequestrant or ezetimibe is recommended.

Clinical trials have demonstrated that monotherapy with ezetimibe significantly lowers total cholesterol, LDL-C, apolipoprotein B and triglycerides, as well as increases HDL-C compared to placebo. Complementary effects on various lipid/lipoprotein parameters were also observed in clinical trials when ezetimibe was coadministered with colesevelam, fenofibrate, niacin and statins.

Dr. Hisel concluded that the effects of ezetimibe given either alone or in addition to a statin or fenofibrate on cardiovascular morbidity and mortality have not been established. Ezetimibe should be available as adjunctive therapy through the medical justification portion of the prior authorization process.

Therefore, all brand cholesterol absorption inhibitors within the class reviewed are comparable to each other and to the generics and OTC products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

No brand cholesterol absorption inhibitor is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

Dr. Ferris commented that statins are recommended as first-line therapy because studies have demonstrated a reduction in cardiovascular endpoints, including mortality, myocardial infarction and stroke. Studies with some lipid-lowering drugs have only evaluated surrogate endpoints, such as cholesterol reduction or carotid intima-media thickness. However, it is thought that the reduction in cholesterol leads to the positive effects on morbidity and mortality. Dr. Hisel agreed with Dr. Ferris and stated that there is an ongoing study evaluating cardiovascular endpoints with simvastatin/ezetimibe compared to simvastatin alone.

There were no further discussions on the agents in this class. Dr. Culpepper asked the P&T Committee Members to mark their ballots.

Fibric Acid Derivatives: AHFS 240606
Manufacturer comments on behalf of these products:
None

Dr. Hisel commented that the fibric acid derivatives that are included in this review are listed in Table 1. Fenofibric acid was approved by the FDA since this class was last reviewed; however, it was reviewed as a new drug by the P&T Committee in August 2009. The fibric acid derivatives are approved for the treatment of hypertriglyceridemia, primary hypercholesterolemia and mixed dyslipidemia. All of the agents are available in a generic formulation, with the exception of the nanocrystallized formulation of fenofibrate.

Guidelines for the treatment of lipid disorders identify LDL-C as the primary target of cholesterol lowering therapy. The HMG-CoA reductase inhibitors (statins) are generally considered first-line therapy in addition to therapeutic lifestyle changes. Fibric acid derivatives have an adjunctive role in the treatment of patients with high triglycerides and low HDL-C, especially in combination with a statin. For patients with very high triglycerides ($\geq$500 mg/dl), treatment with a fibric acid

derivative or niacin should be implemented before LDL-lowering therapy to prevent pancreatitis. Guidelines do not give preference to one fibric acid derivative over another.

Clinical trials have demonstrated that the fibric acid derivatives can effectively lower triglycerides and increase HDL-C, as well as positively impact other lipid/lipoprotein parameters. Complementary lipid effects were also observed in clinical trials when fibric acid derivatives were coadministered with ezetimibe and statins. However, the effect of fibric acid derivatives on cardiovascular morbidity and mortality has not been determined.

Dr. Hisel concluded that there is insufficient evidence to support that one brand fibric acid derivative is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand fibric acid derivatives within the class reviewed are comparable to each other and to the generics and OTC products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

No brand fibric acid derivative is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

There were no further discussions on the agents in this class. Dr. Culpepper asked the P&T Committee Members to mark their ballots.

HMG-CoA Reductase Inhibitors: AHFS 240608
Manufacturer comments on behalf of these products:
Simcor® - Abbott
Lipitor® - Pfizer
Vytorin® - Merck

Dr. Hisel commented that the HMG-CoA reductase inhibitors that are included in this review are listed in Table 1. This includes single entity agents, as well as fixed-dose combination products. Niacin/simvastatin was approved by the FDA since this class was last reviewed; however, it was reviewed as a new drug by the P&T Committee in December 2008. Pitavastatin (Livalo®) was recently added to Medicaid's drug file in May 2010 and will not be included in this review. Alabama Medicaid's policy states that drugs must be commercially available for a minimum of 180 days to be eligible for inclusion in a PDL review.

The HMG-CoA reductase inhibitors (statins) are approved for the treatment of a variety of lipid disorders, including primary hypercholesterolemia, mixed dyslipidemia and hypertriglyceridemia. The fixed-dose combination products are indicated for use when dual therapy is appropriate. Statins can decrease LDL-C by 18% to 60% and triglycerides by 7% to 30%, as well as increase HDL-C by 5% to 15% when administered as monotherapy. Lovastatin, pravastatin and simvastatin are available in a generic formulation.

Guidelines for the treatment of lipid disorders identify LDL-C as the primary target of cholesterol lowering therapy. The statins are generally considered first-line therapy in addition to therapeutic lifestyle changes. If the LDL-C goal is not achieved after 6 weeks of therapy, then the dose of the statin should be increased or another LDL-C lowering drug should be added to the regimen. Guidelines do not give preference to one statin over another.

Numerous clinical trials have demonstrated that the statins can effectively lower LDL-C, non-HDL-C, total cholesterol and triglycerides, as well as positively impact other lipid/lipoprotein parameters. Studies have also demonstrated that aggressive lipid-lowering with a statin allows patients to reach their NCEP ATP III LDL-C goals. Many studies have compared active treatment to placebo or compared combination therapy to monotherapy. In these studies, the more aggressive treatment regimens often improved lipid parameters to a greater extent than the less-intensive treatment regimens. The statins differ in their potency and their effects on LDL-C are dose-dependent. In general, the combination products do not offer any significant clinical advantage over coadministration of their individual components.

All of the statins have been shown to have beneficial effects on coronary heart disease (CHD) outcomes. Atorvastatin, lovastatin, pravastatin, rosuvastatin and simvastatin have been shown to reduce cardiovascular events in patients without CHD, but with multiple risk factors. Atorvastatin, fluvastatin, pravastatin and simvastatin have also been shown to reduce cardiovascular events in patients with clinically evident CHD. In addition, fluvastatin, lovastatin, pravastatin and rosuvastatin have been shown to slow the progression of coronary atherosclerosis in patients with CHD. Studies have demonstrated that statins also decrease the risk of stroke. No incremental benefit of the combination products on cardiovascular morbidity and mortality has been established over and above that demonstrated for statin monotherapy.

Dr. Hisel concluded that there is insufficient evidence to support that one brand HMG-CoA reductase inhibitor is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand HMG-CoA reductase inhibitors within the class reviewed are comparable to each other and to the generics and OTC products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

No brand HMG-CoA reductase inhibitor is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

Dr. Sawyer asked if there are any studies with lipid lowering agents in the pediatric population. Dr. Hisel confirmed that studies have been conducted in this population. Dr. Culpepper stated that she has not had to initiate lipid-lowering therapy in her patient population as she employs diet and exercise strategies.

Dr. Sawyer commented that there is some literature to suggest that the risk of myalgia and myopathy is lower in patients with a normal vitamin D level.

Dr. Ferris asked if the risk of myalgia/myopathy with the statins is related to the dose administered or the strength of the tablet. Dr. Hisel commented that there are a variety of factors that may contribute to the development of myalgia/myopathy, including dose, drug-drug interactions, type of statin used and comorbidities.

There were no further discussions on the agents in this class. Dr. Culpepper asked the P&T Committee Members to mark their ballots.

Antilipemic Agents, Miscellaneous: AHFS 240692
Manufacturer comments on behalf of these products:
Niaspan® - Abbott

Dr. Hisel commented that niacin and omega-3 acid ethyl esters are the only miscellaneous antilipemic agents that are included in this review. Prescription niacin and omega-3 acid ethyl esters are approved by the FDA for the treatment of hypertriglyceridemia. Prescription niacin is also approved for the treatment of primary hypercholesterolemia and mixed dyslipidemia. Niacin is available over-the-counter in immediate-release and sustained-release formulations, which are currently on the Alabama Medicaid Preferred Drug List. Niacin is also available by prescription as immediate-release and extended-release formulations. Omega-3 acid ethyl esters is only available by prescription. There are no generic formulations currently available for prescription niacin or omega-3 acid ethyl esters.

Guidelines for the treatment of lipid disorders identify LDL-C as the primary target of cholesterol lowering therapy. The HMG-CoA reductase inhibitors (statins) are generally considered first-line therapy in addition to therapeutic lifestyle changes. For patients who cannot achieve LDL-C goals with the use of a statin alone, the addition of another LDL-C lowering drug such as niacin, a bile acid sequestrant or ezetimibe is recommended. In high-risk patients with high triglycerides or low HDL-C, consideration can be given to combination therapy with fibrates or niacin and an LDL-lowering agent. If triglycerides are very high ($\geq$500 mg/dl), triglyceride-lowering drugs are first-line therapy. When used at higher doses, omega-3 fatty acids lower triglycerides and are considered an alternative to fibrates or niacin for the treatment of hypertriglyceridemia. Clinical trials suggest that relatively high intakes of omega-3 fatty acids in the form of fish, fish oils, or high-linolenic acid oils will reduce risk for major coronary events in persons with established coronary heart disease.

Niacin is the most effective agent for modifying all lipid abnormalities associated with atherogenic dyslipidemia, and it is the most effective agent for raising HDL-C. Clinical trials have demonstrated that niacin positively impacts a variety of lipid/lipoprotein parameters. Niacin has been shown to reduce the risk of recurrent nonfatal myocardial infarction in patients with hypercholesterolemia, as well as slow the progression or promote regression of atherosclerotic disease in patients with a history of coronary artery disease and hypercholesterolemia. There are limited head-to-head studies comparing the efficacy and safety of the different niacin formulations. While flushing may be more common with the immediate-release formulation, it still occurs with the sustained-release and extended-release products. Cases of severe hepatic toxicity have occurred in patients who have substituted sustained-release niacin products for immediate-release niacin at

equivalent doses. Due to significant safety concerns, the AHA stresses that dietary supplement niacin must not be used as a substitute for prescription niacin, and should not be used for cholesterol lowering due to the potential for very serious side effects.

Clinical trials have demonstrated that prescription omega-3 acid ethyl esters can effectively lower triglycerides, as well as positively impact other lipid/lipoprotein parameters when used as monotherapy or in combination with fenofibrate or statins. The effect of prescription omega-3 acid ethyl esters on cardiovascular mortality and morbidity in patients with elevated triglycerides has not been determined.

Dr. Hisel concluded that prescription niacin products offer significant clinical advantages in general use over the other brands, generics and OTC niacin products in the same class (if applicable), but are comparable to each other. Due to its limited FDA-approved indications, prescription omega-3 acid ethyl esters should be available through the medical justification portion of the prior authorization process for adults with severe hypertriglyceridemia ($\geq$500 mg/dl).

Prescription niacin is recommended for preferred status. Alabama Medicaid should work with manufacturers on cost proposals so that at least one brand prescription niacin product is selected as a preferred agent.

No brand omega-3 acid ethyl ester is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

Dr. Ferris asked if there were any additional advantages with using the sustained-release niacin products over the immediate-release products, other than differences in flushing. Dr. Hisel commented that there are limited head-to-head studies comparing the efficacy and safety of the different niacin formulations.

There were no further discussions on the agents in this class. Dr. Culpepper asked the P&T Committee Members to mark their ballots.

Nitrates and Nitrites: AHFS 241208
Manufacturer comments on behalf of these products:
None

Dr. Hisel commented that the nitrates and nitrites that are included in this review are listed in Table 1, and all of the products are available in a generic formulation. There have been no major changes in the prescribing information, treatment guidelines or clinical studies since this class was last reviewed.

Therefore, all brand nitrates or nitrites within the class reviewed are comparable to each other and to the generics and OTC products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

No brand nitrate or nitrite is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

There were no further discussions on the agents in this class. Dr. Culpepper asked the P&T Committee Members to mark their ballots.

At 10:38 a.m., Dr. Culpepper called for a 10-minute break. The meeting resumed at 10:50 a.m.

7. RESULTS OF VOTING ANNOUNCED

The results of voting were announced and all classes were approved as recommended. Results of voting are described in the Appendix to the minutes.

8. NEW BUSINESS

Dr. Littlejohn stated that the CDC released information on August 10, 2010 regarding the influenza virus. The neuraminidase inhibitors (Relenza® and Tamiflu®) are still recommended for the treatment of influenza. The adamantanes are not recommended due to resistance to these agents. The Agency will continue to leave Relenza® and Tamiflu® in preferred status.

Dr. Littlejohn commented that there was an outstanding agenda item that needed to be addressed by the P&T Committee, which pertained to the preferred status of generic methadone. The DUR Board recommended in April 2009 that the P&T Committee reevaluate the efficacy/safety of methadone, and consider requiring prior authorization for the generic product. She reminded members that this was previously discussed in November 2009, and the Committee elected to wait until the FDA finalized their Risk Evaluation and Mitigation Strategy (REMS) before making any further recommendations. Dr. Hisel stated that the FDA released a statement in July 2010, which recommended additional provider and patient education strategies for the long-acting opioids. Dr. Littlejohn asked the Committee for their recommendation regarding the preferred status of methadone. The Committee discussed the available efficacy/safety data, current and historical utilization trends, as well as the steps that the Agency has taken to educate providers. A motion was made by Mr. Main to maintain the current preferred status of generic methadone and monitor utilization, which was seconded by Dr. Woodruff. Dr. Littlejohn stated that the opiate agonists are scheduled to be re-reviewed in May 2011 and the Committee agreed that methadone utilization should be revisited at that time.

It was announced that a vote would be made for a new Vice-Chair. Mr. Main and Dr. Culpepper respectively requested that their names be removed from the ballot. Ms. LaTonage Porter was selected as the new Vice-Chair.

9. NEXT MEETING DATE

The next P&T Committee Meeting is scheduled for 9:00 a.m. on November 10, 2010 at the Medicaid Building in the Commissioner's Board Room. Additional meetings will be held on February 9, 2011, May 11, 2011, August 10, 2011 and November 9, 2011.

10. ADJOURN

There being no further business, Mr. Main moved to adjourn, and Dr. Ferris seconded.

The meeting was adjourned at 11:25 a.m.

Appendix

RESULTS OF THE BALLOTING
Alabama Medicaid Agency
Pharmacy and Therapeutics Committee
August 11, 2010

A. **Recommendation:** No brand genitourinary smooth muscle relaxant is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

Amendment: None

Vote: Unanimous to approve as recommended

R Moorhead — ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action
Medical Director

Kathy Hall — ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action
Deputy Commissioner

Carol H. Steckel — ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action
Commissioner

B. **Recommendation:** No brand platelet-aggregation inhibitor is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

Amendment: None

Vote: Unanimous to approve as recommended

R Moorhead — ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action
Medical Director

Kathy Hall — ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action
Deputy Commissioner

Carol H. Steckel — ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action
Commissioner

C. **Recommendation:** No brand antiarrhythmic agent is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

Amendment: None

Vote: Unanimous to approve as recommended

R Moore MD ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action
Medical Director

Kathy Kelly ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action
Deputy Commissioner

Carol H. Steckel ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action
Commissioner

D. **Recommendation:** No brand cardiotonic agent is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

Amendment: None

Vote: Unanimous to approve as recommended

R Moore MD ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action
Medical Director

Kathy Kelly ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action
Deputy Commissioner

Carol H. Steckel ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action
Commissioner

E. **Recommendation:** No brand miscellaneous cardiac drug is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

Amendment: None

Vote: Unanimous to approve as recommended

R Moon MD ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action
Medical Director

Kathy Hall ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action
Deputy Commissioner

Carol H. Steckel ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action
Commissioner

F. **Recommendation:** No brand bile acid sequestrant is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

Amendment: None

Vote: Unanimous to approve as recommended

R Moon MD ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action
Medical Director

Kathy Hall ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action
Deputy Commissioner

Carol H. Steckel ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action
Commissioner

G. **Recommendation:** No brand cholesterol absorption inhibitor is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

Amendment: None

Vote: Unanimous to approve as recommended

P Moorms ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action
Medical Director

Kathy Hall ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action
Deputy Commissioner

Carol H Steckel ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action
Commissioner

H. **Recommendation:** No brand fibric acid derivative is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

Amendment: None

Vote: Unanimous to approve as recommended

P Moorms ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action
Medical Director

Kathy Hall ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action
Deputy Commissioner

Carol H. Steckel ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action
Commissioner

I. **Recommendation:** No brand HMG-CoA reductase inhibitor is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

Amendment: None

Vote: Unanimous to approve as recommended

P Thomas ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action
Medical Director

Kathy Kelly ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action
Deputy Commissioner

Carol H. Steckel ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action
Commissioner

J. **Recommendation:** Prescription niacin is recommended for preferred status. Alabama Medicaid should work with manufacturers on cost proposals so that at least one brand prescription niacin product is selected as a preferred agent.

No brand omega-3 acid ethyl ester is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands

Amendment: None

Vote: Unanimous to approve as recommended

P Thomas ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action
Medical Director

Kathy Kelly ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action
Deputy Commissioner

Carol H. Steckel ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action
Commissioner

K. **Recommendation:** No brand nitrate or nitrite is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

Amendment: None

Vote: Unanimous to approve as recommended

☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action
Medical Director

☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action
Deputy Commissioner

☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action
Commissioner

Respectfully submitted,

August 11, 2010

Tina Hisel, Pharm.D., BCPS